Case Report

Central apnoea after balanced general anaesthesia that included dexmedetomidine

A. M.-H. Ho*, S. Chen and M. K. Karmakar

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, PRC

*Corresponding author. E-mail: hoamh@hotmail.com

Dexmedetomidine is an \( \alpha_2 \)-adrenoreceptor agonist that, in spite of its potent sedative, amnesic, and analgesic properties, has minimal respiratory depressant effect. Even at doses adequate for general anaesthesia, it does not cause central apnoea. Thus, it has been claimed that ‘combining \( \alpha_2 \)-agonists with opiate narcotics or non-steroidal anti-inflammatory drugs can enhance the analgesic efficacy without increasing the respiratory depressant effect of the latter’ and ‘the combination of \( \alpha_2 \)-adrenoceptor agonists with opioids does not lead to further ventilatory depression’. We present a case of central apnoea after general anaesthesia that included opioids and dexmedetomidine, and remind the readers that in susceptible patients, dexmedetomidine may cause life-threatening respiratory depression through potentiation of co-administered central nervous system depressants.


Keywords: agonists, \( \alpha_2 \)-adrenergic; complications, apnoea; complications, respiratory failure; opiates; premedication, dexmedetomidine

Accepted for publication: September 12, 2005

Dexmedetomidine (Precedex; Abbott Laboratories, Abbott Park, IL, USA) has potent sympatholytic, analgesic, and sedative properties,\(^1\)–\(^12\) mediated through \( \alpha_2 \)-adrenoceptors in the central and peripheral nervous systems, in autonomic ganglia at pre- and post-synaptic sites, and at the locus coeruleus.\(^8\)\(^,\)\(^11\) One of the most important advantages of dexmedetomidine is the lack of significant respiratory depression.\(^1\)–\(^8\)\(^,\)\(^12\) As such, it has been used for sedation in the intensive care unit and for weaning from respiratory support.\(^7\)\(^,\)\(^9\) It reduces the MAC of potent inhalational anaesthetics\(^1\) and is morphine-sparing.\(^7\)\(^,\)\(^9\)\(^,\)\(^10\) Even at doses high enough to be used as a sole general anaesthetic agent, dexmedetomidine did not cause any significant respiratory depression.\(^6\) We report the case of a patient who suffered central apnoea in the post-anaesthetic care unit after a general anaesthetic that included opioids and dexmedetomidine.

Case report

A 69-yr-old, 64-kg, 153-cm Chinese woman was scheduled to undergo vaginal hysterectomy, repair of cystocele and enterocoele, MaCall’s culdoplasty, perineoplasty, and vaginal taping. Comorbidity included controlled hypertension (treated with nifedipine and enalapril) but no cardiorespiratory, neurological, or neuromuscular disease. There was no history of regular sedative, psychotropic or recreational drug, or analgesic use. Her preoperative ECG and blood tests were all normal. She received no preoperative sedation.

After placement of routine monitors (bispectral index monitor not included) and preoxygenation of the lungs, general anaesthesia was induced with fentanyl 100 \( \mu \)g, propofol 120 mg, and rocuronium 35 mg, and the patient’s trachea was intubated. Maintainance was with \( \text{N}_2\text{O} \) and isoflurane 0–1%. Ten minutes after induction of anaesthesia, shortly before the first surgical stimulation, morphine 7.5 mg, the only dose for the case, was given as a bolus. Fifty-five minutes after induction the isoflurane was switched off, and dexmedetomidine was started as per a previously published and apparently effective protocol\(^10\): 60 \( \mu \)g was given over 30 min, followed by an infusion of 0.5 \( \mu \)g kg\(^{-1}\) h\(^{-1}\). Surgery was completed sooner than expected. Intraoperative blood loss was 200 ml. Just before transport to the post-anaesthetic care unit, the patient’s end-tidal isoflurane, \( \text{N}_2\text{O} \), and \( \text{CO}_2 \) were 0%, 3%, and 48–50 mm Hg, respectively. She was breathing spontaneously with a tidal volume of 380–420 ml and ventilatory frequency of
10 min$^{-1}$, had normal vital signs, and had only reacted transiently and mildly to the tracheal tube. Muscle relaxation had been fully reversed (two strong twitches on train-of-four stimulation to ulnar nerve before reversal with standard doses of atropine and neostigmine). She was not responsive when her name was called. The patient left theatre 40 min after commencement of dexmedetomidine. Five minutes later she started to cough on the tracheal tube and attempted to open her eyes when her name was called. The tracheal tube was removed and an O$_2$ facemask was applied. Within 1 min of extubation, she stopped breathing and her $S_p_{O_2}$ quickly deteriorated. There was no respiratory effort detectable. She did not respond to verbal stimulation. She was immediately hand-mask-bag-ventilated and her $S_p_{O_2}$ came from a low of 81% quickly back to 99%. During the apnoeic episode, the dexmedetomidine infusion was discontinued. She started to breath on her own again about 5 min later and opened her eyes to verbal stimulation another 5 min later. She made an uneventful recovery.

**Discussion**

Dexmedetomidine, a highly selective α$_2$-agonist, induces analgesia, sympathetic, and sedation that partially mimics natural sleep. Evidence suggests that, unlike most other powerful sedatives and analgesics, it has minimal respiratory depressing properties.

In dogs and rabbits, dexmedetomidine caused moderate dose-dependent respiratory depression but a paradoxical increase in ventilation at high doses.

In controlled settings, dexmedetomidine 0.25, 0.5, and 1 µg kg$^{-1}$ infused over 2 min in healthy volunteers (age 18–45 yr) resulted in a mild and dose-dependent reduction in ventilation. However, at 2 µg kg$^{-1}$, ventilation paradoxically was less depressed. In healthy men (age 21–40 yr) given stepwise target infusion plasma dexmedetomidine concentrations of 0.6, 1.2, 1.8, and 2.4 ng ml$^{-1}$, the ventilatory frequency increased in a dose-dependent manner, which more than compensated for the slight reductions in tidal volume. The $S_p_{O_2}$, and blood pH did not change. In non-medicated men (age 20–27 yr) given target infusions of 0.5–8.0 ng ml$^{-1}$, $P_{A_{CO_2}}$ increased by 3–4 mm Hg at the higher concentrations.

Clinical experience is consistent with the respiratory-sparing sedative effect of the drug. Ramsay and Luteran described the use of i.v. dexmedetomidine as the sole anaesthetic agent. They gave 1 µg kg$^{-1}$ plus an infusion of 10 µg kg$^{-1}$ h$^{-1}$ plus topical airway anaesthesia to a 66-yr-old woman with subglottic stenosis for laser treatment. The patient required chin support. On room air, the $S_p_{O_2}$ was 94–98%, and $P_{A_{CO_2}}$ was 43 mm Hg. A 65-yr-old man with emphysema underwent resection of facial lesions with full-thickness skin grafting receiving only dexmedetomidine 1 µg kg$^{-1}$ loading plus an infusion of less than 5 µg kg$^{-1}$ h$^{-1}$, presumably with local anaesthetic coverage. On room air, his $S_p_{O_2}$ was greater than 90% throughout. A 50-yr-old man underwent rigid and fibroptic bronchoscopy, laryngoscopy, bronchopulmonary lavage, and revision of a tracheal prosthesis, receiving only dexmedetomidine 1 µg kg$^{-1}$ plus an infusion of less than 5 µg kg$^{-1}$ h$^{-1}$. On room air, his $S_p_{O_2}$ was greater than/equal to 92%.

In the ICU setting, dexmedetomidine 1 µg kg$^{-1}$ given over 10 min plus an infusion of 0.2–0.7 µg kg$^{-1}$ h$^{-1}$, compared with placebo, in post-surgical patients resulted in, respectively, a 80% and a more than 50% reduction in midazolam and morphine requirement, with no difference in the level of sedation, $P_{A_{CO_2}}$, and blood pH.

Tritsch and colleagues gave dexmedetomidine (1 µg kg$^{-1}$ over 10 min plus 0.1–0.7 µg kg$^{-1}$ h$^{-1}$) or placebo to post-surgical patients on admission to the ICU. Dexmedetomidine-treated patients required 57 and 27% of the propofol requirements during mechanical ventilation and weaning, respectively, and 41% of the morphine to achieve the same bispectral indices as controlled patients. Time to extubation did not differ between the groups, both of which had three cases of respiratory failure out of 15 patients.

After major abdominal surgery, dexmedetomidine 1 µg kg$^{-1}$ loading over 10 min plus 0.4 µg kg$^{-1}$ h$^{-1}$ infusion resulted in 66% reduction in morphine consumption in the PACU with no significant change in the RR and $S_p_{O_2}$. In summary, in young healthy volunteers, dexmedetomidine, even at high doses, induces sedation with minimal respiratory effect during quiet, unchallenged breathing, and variable but somewhat blunted ventilatory responses to hypercapnia and hypoxia. Likewise, clinical evidence also points to the α$_2$-agonist as a potent sedative and analgesic without significant central respiratory depression, even at very high doses, albeit occasionally causing obstructive apnoea. This unique combination of effects is also a characteristic of clonidine, another α$_2$-agonist. It has thus been claimed that ‘combining α$_2$-agonists with opiate narcotics or non-steroidal anti-inflammatory drugs can enhance the analgesic efficacy without increasing the respiratory depressive effect of the latter’, and ‘the combination of α$_2$ adrenoceptor agonists with opioids does not lead to further ventilatory depression’. Our case challenges this notion.

This case of central apnoea sounds a cautionary note that dexmedetomidine, notwithstanding its unique and favourable respiratory effect profile, is ultimately a potent sedative and analgesic. Sedation and normal sleep lead to variable degrees of analgesia, muscle hypotonia, and amnesia due to changing aminergic-cholinergic balance in the pons, explaining in part why sleep- and hypnosis-inducing agents are opioid-sparing. In sleep and sedation and as one ages, the hypercapnic ventilatory response is reduced. Agents that induce sleep or sedation, such as barbiturates, benzodiazepines, and α$_2$-adrenergic agonists, thus may all potentiate the ventilatory depressive effect of opiates, especially in the elderly. Moreover, ventilatory drive is modulated in part by the intensity on the brainstem of nociceptive inputs.
which are depressed by hypnotics and analgesics. This mutually enhancing respiratory depressant effect between opioids and sedating agents is well known to anaesthetists—a heavily sedated patient can go from minimal respiratory depression to apnoea with just a small dose of narcotic.

Based on the above arguments, we speculate that the main cause of our patient’s apnoea was likely the combined effects of dexmedetomidine, morphine, and fentanyl. Contributory factors included the patient’s age, the low level of post-surgical and post-extubation noxious stimulation, the lack of a history of habitual sedative use, and possibly her ethnicity. Her arterial CO₂ and serum glucose and electrolytes, although not measured, probably had no bearing on her central apnoea. She was not paralysed, dehydrated, septic, and had, in all likelihood, not suffered from seizure or an intracranial event.

Compared with patients receiving morphine alone, patients given dexmedetomidine require 50–66% less morphine. Using this degree of morphine sparing capability as a rough guide, it would be akin to having given this elderly Chinese opiate-naïve lady rather large doses of opioids, some 19 mg of morphine and some 250 mg of fentanyl at 90 and 100 min, respectively, before the respiratory arrest.

In conclusion, although by itself, dexmedetomidine, even at high doses, possesses only minimal central respiratory depressant properties, it may, through its potent sedative and analgesic actions, greatly potentiate the respiratory depressant properties of co-administered sedatives and analgesics, especially in patients who are more susceptible.

References

6 Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology 2004; 101: 787–90
8 Ebert T, Maze M. Dexmedetomidine: another arrow for the clinician’s quiver. Anesthesiology 2004; 101: 568–70
12 Khan ZP, Ferguson CN, Jones CM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anesthesiology 1999; 85: 455–60